REMARKS

Rejection of Claims 2, 5, 6 and 41-43 under 35 U.S.C. §101

Claims 2, 5, 6, and 41-43 are rejected under 35 U.S.C. §101 "for the reasons previously set forth in Paper No. 14, Section 3, pages 2-3" (Office Action, page 2).

The Examiner notes that in the Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132,(the Haupert Declaration) Dr. Haupert "declares that a two-tailed T test of the 70 micromolar point determined that when the inhibitor was digoxin at 50 and 100 ***mM***, the result was p=0.16 and 0.18" which is not different from zero inhibition" (Office Action, page 2). The Examiner notes that the "data presented was drawn to 70 micromolar, not millimolar, thus the Declaration is not commensurate in scope with the claimed invention" (Office Action, pages 2-3).

Applicants appreciate the Examiner's careful reading of the Haupert Declaration. The Haupert Declaration contains a typographical error. The sentence "When the inhibitor was digoxin at 50 and 100 ***mM***, the result was p = 0.16-0.18." However, the sentence should read "When the inhibitor was digoxin at 50 and 100 ***μM***, the result was p = 0.16-0.18." Applicants are in the process of preparing a Second Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132, (the Second Haupert Declaration) to address this typographical error.

The Examiner further states that "since no datapoint was presented at 100 micromolar and 'wobble' was found at 70 micromolar, it would be expected that inhibition would only increase from 70 to100 micromolar" and [g]iven the information in the specification, it would not be expected that the binding of the antibodies to ouabain would not be inhibited by about 100 micromolar of digoxin and the invention appears to be inoperative" (Office Action, page 3).

Applicants respectfully disagree. In the Haupert Declaration, Dr. Haupert states that for the 1-10 and 8E4 monoclonal antibodies, "the digoxin values clustered at the highest dose point in Figure 6 are in fact not different from zero inhibition" (the Haupert Declaration, page 3). Furthermore, in the specification as filed, Applicants show that the cross reactivity of monoclonal antibodies 7-1 and 1-10 with digoxin was "***absent***", in that "their binding to Oua-BGG could not be inhibited with concentrations as high as 100 μM of free Dig" in Figure 3 (specification, page 22, lines 18-20, Figure 3).

The Examiner states that a "review of the specification, Figure 3 demonstrates that antibody 5A12 is inhibited by digoxin at less than about 50 micromolar digoxin", and thus, the Examiner concludes that the invention of Claims 41-43 is inoperative (Office Action, page3).

Applicants respectfully disagree. The x axis of Figure 3 is a logarithmic scale, and a careful reading of the x axis indicates that about 50 μM digoxin does not inhibit monoclonal antibody 5A12 from binding to ouabain.

Clearly the claimed invention is operative.

Rejection of Claims 2, 5, 6 and 41-43 under 35 U.S.C. §112, first paragraph

Claims 2, 5, 6 and 41-43 are rejected under 35 U.S.C. §112, first paragraph "for the reasons previously set forth in Paper No. 14, Section 5, page 3" (Office Action, page 3). It is the Examiner's opinion that since the claimed invention is inoperative, "one of skill in the art would not know how to make and use the claimed invention with a reasonable expectation of success" (Office Action, pages 3-4).

Applicants respectfully disagree. As pointed out above, the claimed invention is operative. In the Haupert Declaration, Dr. Haupert states that for the 1-10 and 8E4 monoclonal antibodies, "the digoxin values clustered at the highest dose point in Figure 6 are in fact not different from zero inhibition" (the Haupert Declaration, page 3). Furthermore, in the specification as filed, Applicants show that the cross reactivity of monoclonal antibodies 7-1 and 1-10 with digoxin was "***absent***", in that "their binding to Oua-BGG could not be inhibited with concentrations as high as 100 μM of free Dig" in Figure 3 (specification, page 22, lines 18-20, Figure 3). Finally, the x axis of Figure 3 is a logarithmic scale which indicates that about 50 μM digoxin does not inhibit monoclonal antibody 5A12 from binding to ouabain.

Clearly the claimed invention is operative, and thus, Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 2, 5, 6, 41-43, 45-48 and 53-55 under 35 U.S.C. §112, first paragraph

Claims 2, 5, 6, 41-43, 45-48 and 53-55 are rejected under 35 U.S.C. §112, first paragraph because Applicant has not addressed the issue drawn to "replacement of the deposit if viable samples cannot be dispensed by the depository as required" (Office Action, page 4).

Applicants are filing concurrently a Statement Under 37 C.F.R. §1.805(a), thereby overcoming the rejection.

Rejection of Claims 1, 3, 4, 39, and 49-51 under 35 U.S.C. §102(b)

Claims 1, 3, 4, 39 and 49-51 are rejected under 35 U.S.C. §102(b) as being anticipated by the Lin *et al.* reference. In response to Applicants' position stated in the previously filed Amendment, the Examiner states that "the claims are drawn to inhibition by digoxin and not to inhibition by BSA or HSA and it is clear that the plasma digoxin did not inhibit binding of the antibody to ouabain, thus the limitations drawn to digoxin inhibition are met absent evidence to the contrary that the claimed product is different from that taught by the prior art and to establish patentable differences" (Office Action, pages 4-5).

Applicants respectfully disagree. Applicants' claimed invention is directed to a monoclonal antibody or antigen binding fragment thereof having ***binding specificity for ouabain***, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin. There is no teaching in the Lin *et al.* reference that the plasma digoxin did not inhibit binding of the antibody to ouabain. Nevertheless, as pointed out in the previously filed Amendment, Lin *et al.* do not teach a monoclonal antibody having binding specificity for ouabain, the monoclonal antibody of Lin *et al.* has ***binding specificity for a ouabain-BSA conjugate***.

Lin *et al.* injected Balb/C mice with a ouabain-BSA conjugate (Oua-BSA) and spleens cells from mice showing the "***highest titer against ouabain-BSA***" were selected for fusion" (Lin *et al.*, page 131, column 2, emphasis added). In Figure1, Lin *et al.* provide a schematic of the monoclonal antibody-based immunoassay for ouabain (Lin *et al.*, Figure 1, Method II). Lin *et al.* clearly state that:

> Method II (in Fig. 1) shows a different approach for the OLF determination using a mouse ouabain specific monoclonal antibody against sample OLF or ***against the immobilized ouabain-BSA*** on the microtiter plate (Lin *et al.*, page 132, column 2, Figure 1, emphasis added).

Clearly, Lin *et al.* do not disclose a monoclonal antibody or antigen binding fragment thereof having ***binding specificity for ouabain***, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin.

The Examiner invites Applicants to "submit objective evidence, demonstrating that the prior art antibody is different than the claimed antibody.

As pointed out in the previously filed Amendment, objective evidence demonstrating that the Lin *et al.* antibody is different than Applicants' claimed antibody (*i.e.*, the Lin *et al.* antibody does not have ***binding specificity for ouabain***) is in the specification as filed. Initially, Applicants injected Balb/C mice with a ouabain-BSA conjugate (Oua-BSA), which is the method Lin *et al.* used. Applicants teach that:

> In an attempt to produce Oua-specific mAbs, Oua was coupled to different protein carriers. From the fusion of spleen cells of A/J and ***Balb/C*** mice which were immunized with ***Oua-BSA***, Oua-HSA or Oua-BGG ***over 1000 clones exhibited significant specific binding to Oua-protein conjugates*** (specification, page 21, lines 12-15).

Thus, Applicants developed a ***novel*** method in order to produce a monoclonal antibody or antigen binding fragment thereof having ***binding specificity for ouabain***, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin. Applicants coupled Oua "to the antidigoxin 26-10 mAB which was derived from A/J mice . . . and then hyperimmunized A/J mice with Oua-26-10 Ab conjugate" (specification, page 21,lines 19-22). Applicants screened 600 clones, three of which (*i.e.*, 8E4, 1-10, 7-1) produced a monoclonal antibody or antigen binding fragment thereof having ***binding specificity for ouabain***, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin.

Lin *et al.* clearly do not anticipate Applicants' claimed invention.

Rejection of Claims 1, 3, 4, 38, 39 and 44 under 35 U.S.C. §103

Claims 1, 3, 4, 38 and 39 are rejected under 35 U.S.C. §103 "as being unpatentable over U.S. Patent No. 5,164,296 in view of the Lin *et al.* and Blaustein references. In response to Applicants' position stated in the previously filed Amendment, the Examiner states that "the

references in combination make the claimed invention obvious for reasons of record"; that the arguments are not persuasive for the reasons set forth above"; that *In re Gordon* is not relevant to the instant invention" in that a blood filter assembly "is not an art analogous to the antibody art claimed in the instant invention"; and that "the antibody of the combined reference binds to an epitope on ouabain and therefore has binding specificity for ouabain" (Office Action, page 5-6). The Examiner concludes that "the references in combination make obvious the claimed invention for the reasons of record" (Office Action, page 6).

Applicants respectfully disagree. Even if the antibody produced by combining the teachings of U.S. Patent No. 5,164,296 (Blaustein *et al.*) in view of the Lin *et al.* and Blaustein "binds to an epitope on ouabain" it does not do so with specificity, and thus, the combined teachings of the cited art do not teach a monoclonal antibody or antigen binding fragment thereof having ***binding specificity for ouabain***.

As pointed out above, in order to produce a ***novel*** monoclonal antibody that has binding specificity for ouabain wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin, Applicants had to develop a ***novel*** method to do so. Specifically, Applicants immunized mice with ouabain conjugated to ***a carrier that is not recognized as foreign in the immunized animal (i.e., an antibody that have previously been produced by the immunized animal)***. Applicants coupled Oua "to the antidigoxin 26-10 mAB which was derived from A/J mice . . . and then hyperimmunized A/J mice with Oua-26-10 Ab conjugate" (specification, page 21, lines 19-22). Neither Blaustein *et al.*, Lin *et al.* nor Blaustein teaches immunizing mice with a conjugate comprising the immunogen against which an antibody is desired conjugated to ***a carrier that is not recognized as foreign in the animal***. Furthermore, unlike Lin *et al.*, Applicants screened for a mAb having binding specificity for ouabain using ouabain-BGG (*i.e.*, a hapten-carrier conjugate in which the carrier is different than the *carrier* of the hapten-carrier conjugate used to *immunize* the animal).

Blaustein *et al.* teach "***[p]olyclonal anti-ouabain antisera***" which cross reacts with digoxin at 5.2% (Blaustein *et al.*, column 26, line 1; Table 1). Lin *et al.* teach a monoclonal antibody ***against ouabain-BSA***. Blaustein *et al.* describes "evidence that elevated levels of a recently-discovered adrenal cortical hormone, endogenous ouabain, plays a central role" in the

pathogenesis of hypertension (Blaustein, abstract). Blaustein does not teach or suggest anti-ouabain antibodies.

Blaustein *et al.* discuss a method of producing an antibody having binding specificity for ouabain and provide 3 conjugates for doing so (ovalbumin linked to ouabain; poly-D-lysine linked to ouabain; ovalbumin linked to ouabain using a spacer) (Blaustein *et al.*, Example 2, column 22, line 43 - column 23, line 14). Blaustein *et al.* note that "[p]revious attempts to raise ouabain antibodies have used only a single conjugate of ouabain and BSA for initial immunization and subsequent boosters"(Blaustein *et al.*, column 14, lines n42-45), and teach that the "use of a combination of different conjugates (containing different carriers and linking agents) is important for preparing antibodies having binding specificity for ouabain" (Blaustein *et al.*, column 16, lines 40-43). However, Blaustein *et al.* clearly teach that "the carriers and linking agents employed ***are not critical***" and that other carriers such as BSA can be used (Blaustein *et al.*, column 16, lines 50-58, emphasis added).

Thus, at most, the combined teaching of Blaustein *et al.*, Lin *et al.* and Blaustein would direct one of skill in the art to obtain an antibody having binding specificity for ouabain by immunizing an animal with "a combination of different" ouabain conjugates (*e.g.*, Oua-BSA conjugate used by Lin *et al.*). However, as described in the Lin *et al.* reference and in Applicants' specification as filed, such a method does not generate a monoclonal antibody that has binding specificity for ouabain wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin (specification, page 21, lines 11- 18). Such a method generates a monoclonal antibody having binding specificity for the ouabain conjugate. The carrier to which ouabain is linked was critical in obtaining the claimed antibody. Neither Lin *et al.* nor Blaustein teaches that the carrier to which ouabain is linked is critical, and Blaustein *et al.* specifically teach that the carrier to which ouabain is linked is ***not critical***. The combined teaching of Blaustein *et al.*, Lin *et al.* and Blaustein teach away from Applicants' claimed invention.

Thus, the combined teaching of Blaustein *et al.*, Lin *et al.* and Blaustein do not render obvious Applicants' claimed invention.

Rejection of Claims 1, 3, 4, 38, 39 and 44 under 35 U.S.C. §112, first paragraph

Claims 1, 3, 4, 38, 39 and 44 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention" (Office Action, page 6). The Examiner states that "the data presented in the specification clearly shows that the antibodies exemplified do cross react with digoxin and for the reasons set forth above would be expected to cross react with 100 micromolar digoxin" (Office Action, page 7). Citing *Regents of the University of California v. Eli Lilly*, the Examiner states that the "instant disclosure of these cross reacting species of antibodies does not adequately describe the scope of the claimed genus, which encompass all antibodies that do not cross react with digoxin" (Office Action, page 7). It is the Examiner's opinion that "the instant disclosure does not describe a single monoclonal antibody that binds to ouabain which is not inhibited by 100 micromolar digoxin" (Office Action, page 7).

Applicants respectfully disagree. The *Regents of the University of California v. Eli Lilly* case is directed to DNA. As the Examiner has pointed out in response to Applicants' citation of the *In re Gordon* case, it is not an art analogous to Applicants' claimed antibody art, and thus, it is not relevant to Applicants' claimed invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (*Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111,1116 (Fed. Cir. 1991)). Possession may be shown by a description in the specification of an actual reduction to practice of the claimed method (MPEP 2163, page 2100-161). For a genus, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice (MPEP 2163, page 2100-164).

Applicants clearly reduced the invention to practice and in doing so, provide ***three*** monoclonal antibodies that have binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin. As pointed out above, the Haupert Declaration contains a typographical error. The sentence "When the inhibitor was digoxin at 50 and 100 ***mM***, the result was p = 0.16-0.18." However, the sentence should read "When the inhibitor was digoxin at 50 and 100 ***μM***, the result was p = 0.16-0.18."

Applicants are in the process of preparing a Second Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132, (the Second Haupert Declaration) to address this typographical error. Furthermore, in the Haupert Declaration, Dr. Haupert clearly states that for the 1-10 and 8E4 monoclonal antibodies, "the digoxin values clustered at the highest dose point in Figure 6 are in fact not different from zero inhibition" (the Haupert Declaration, page 3). Moreover, in the specification as filed, Applicants show that the cross reactivity of monoclonal antibodies 7-1 and 1-10 with digoxin was "***absent***", in that "their binding to Oua-BGG could not be inhibited with concentrations as high as 100 μM of free Dig" in Figure 3 (specification, page 22, lines 18-20, Figure 3).

In the specification as filed, Applicants reduced the invention to practice using a ***novel*** method to produce a monoclonal antibody or antigen binding fragment thereof having ***binding specificity for ouabain***, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin. Applicants coupled Oua "to the antidigoxin 26-10 mAB which was derived from A/J mice . . . and then hyperimmunized A/J mice with Oua-26-10 Ab conjugate" (specification, page 21,lines 19-22). Applicants clearly describe the method for obtaining the claimed antibodies and methods of screening clones obtained in the method to identify monoclonal antibodies (*e.g.*, 8E4, 1-10, 7-1) having ***binding specificity for ouabain***, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin.

Clearly, in the specification as filed, Applicants' have provided sufficient detail for obtaining monoclonal antibodies that have ***binding specificity for ouabain***, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin, that one of skill in the art would reasonably conclude that Applicants had possession of the full scope of the claimed invention.

Rejection of Claims 1-4, 6, 38 and 40-44 under 35 U.S.C. §112, first paragraph

Claims 1-4, 6, 38 and 40-44 are rejected under 35 U.S.C. §112, first paragraph "as the specification does not contain a written description of the claimed invention" (Office Action, page 8). The Examiner states that "'about 100 micromolar' and 'about 50 micromolar' has no

clear support in the specification and the claims as originally filed" (Office Action, page 8). The Examiner states that "a review of the cited support reveals support for the antibody 5A12, 7-1, 1-10 not being inhibited with concentrations 'as high as 100 micromolar', further there is no mention of Antibody 8E4 not being inhibited by concentrations 'as high as 100 micromolar'" (Office Action, page 8). The Examiner further states that "a review of the cited support reveals no limitation in the cited claims for 'about 50 micromolar' and nothing in figure 3 that points specifically to the newly claimed limitation" (Office Action, page 8).

Applicants respectfully disagree. "Prior to determining whether the disclosure satisfies the written description requirement for the claimed subject matter, the examiner should review the claims and the entire specification including the specific embodiments, ***figures***, and sequence listings to understand how applicant provides support for the various features of the claimed invention" (MPEP, 8th edition, §2163, page 2100-164, emphasis added). In addition, the subject matter of the amended claim need not be described literally or "*in ipsis verbis*" in order for the specification to satisfy the written description requirement of 35 U.S.C.§ 112 (See, *e.g.*, *In re Lukach*, 442 F.2d 967, 969, 169 U.S.P.Q.795,796 (C.C.P.A. 1971).

In the specification as filed, one of skill in the art would clearly understand that the graph in Figure 6 shows that the binding specificity of monoclonal antibodies 1-10 and 8E4 for ouabain is not inhibited by ***about*** 100μM of digoxin. Furthermore, in the specification as filed, one of skill in the art would clearly understand that the graph in Figure 3 shows that the binding specificity of monoclonal antibodies 1-10 and 7-1 for ouabain is not inhibited by ***about*** 100μM of digoxin, and that the binding specificity of monoclonal antibody 5A12 for ouabain is not inhibited by ***about*** 50μM of digoxin.

As pointed out above, the Haupert Declaration contains a typographical error. The sentence "When the inhibitor was digoxin at 50 and 100 ***mM***, the result was p = 0.16-0.18." However, the sentence should read "When the inhibitor was digoxin at 50 and 100 ***μM***, the result was p = 0.16-0.18." Applicants are in the process of preparing a Second Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132, (the Second Haupert Declaration) to address this typographical error. Furthermore, in the Haupert Declaration, Dr. Haupert clearly states that for the 1-10 and 8E4 monoclonal antibodies, "the digoxin values clustered at the highest dose point

in Figure 6 are in fact not different from zero inhibition" (the Haupert Declaration, page 3). Moreover, in the specification as filed, Applicants show that the cross reactivity of monoclonal antibodies 7-1 and 1-10 with digoxin was "***absent***", in that "their binding to Oua-BGG could not be inhibited with concentrations as high as 100 μM of free Dig" in Figure 3 (specification, page 22, lines 18-20, Figure 3).

In the specification as filed (*e.g.*, Figures 3 and 6), Applicants clearly describe monoclonal antibodies having binding specificity for ouabain wherein the binding specificity is not inhibited by about 100μM of digoxin (1-10, 8E4 and 7-1), and a monoclonal antibody having binding specificity for ouabain wherein the binding specificity is not inhibited by about 50μM of digoxin (5A12). Based on the clear teachings in Applicants' specification, one of skill in the art would reasonably conclude that Applicants had possession of the full scope of the claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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